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CORTISONE IN RHEUMATIC CARDITIS: SOME PRELIMINARY OBSERVATIONS

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The dramatic and immediate results achieved in the treatment of rheumatoid arthritis by the use of cortisone and A.C.T.H. was followed by observations on other forms of arthritis, among them rheumatic fever.

Several claims have been made for the beneficial influence of these drugs upon the articular manifestations, pyrexia, and raised sedimentation rate found in acute rheumatism. It was naturally hoped that the preparations might exert a beneficial effect upon the cardiac muscle and fibrous valves affected by rheumatic fever similar to that upon the skeletal muscles and fibrous tissue in rheumatoid arthritis. These hopes were expressed by Hench, Slocumb, *et al.* (1949), who treated three cases of rheumatic fever, noting a rapid disappearance of fever, tachycardia, and arthralgia. The E.S.R. became normal within three to four weeks. They further observed electrocardiographic evidence of improvement. Thus the P-R interval, which was prolonged in two cases, returned to normal within a week, and in one case the RS-T and the T wave changes disappeared in 26 days. The clinical manifestations of carditis in their cases do not appear to have been convincing, and the authors were well aware of this though they hoped that cortisone might favourably influence the course of rheumatic carditis. Further, they thought that the effects of cortisone on other manifestations of rheumatic fever were superior to those obtained by salicylates or in cases allowed to run a natural course. Later work by the same authors seemed to support their original claims (Hench, Kendall, *et al.*, 1950).

Barnes and Smith (1950) also treated five cases and noted the disappearance of fever, tachycardia, and joint pains in a few days. They, too, claimed that the P-R interval tended to revert to normal in the first week of treatment and that tachycardia was succeeded by bradycardia, though the latter disappeared on reduction or withdrawal of cortisone. In one of their cases, after two weeks' treatment, there was a disappearance of physical signs upon which a diagnosis of myocarditis, pericarditis, pulmonary congestion, and pleural effusion had been made.

Another interesting case was that described by Bell, Bell, and Wilson (1950) in which severe rheumatic pericarditis with pneumonitis and congestive cardiac failure was treated with the heavy initial dose of 2,000 mg. of cortisone in 48 hours. During this time pericardial friction and gallop rhythm disappeared and the authors did not notice any untoward symptoms from these large doses. There was, however, a recurrence of symptoms on discontinuing the treatment.

Another small group of cases was beneficially treated by McEwen *et al.* (1950), and larger groups are described by Keith and Neill (1951), 23 cases, and by Coste *et al.* (1950), 15 children. Varying degrees of success are claimed.

By contrast Harris *et al.* (1951), whilst admitting the subsidence of other constitutional manifestations of rheumatic fever, found that the cardiological signs showed no improvement throughout the entire period of observation. They treated four cases.

Videbaek *et al.* (1950) also treated three cases without response to high dosage of cortisone, though they claimed improvement with A.C.T.H.

It is evident, therefore, that there is much conflict of opinion about the influence, if any, of cortisone on the cardiac lesions of rheumatic fever. A decision on this matter is of great importance in view of the crippling effects of this disease in childhood, and the fact that hitherto no treatment has been known to modify the course of the carditis, however effective it may have been in controlling other manifestations.

Suitable cases of rheumatic carditis do not occur often enough for any one group of observers to form firm conclusions about the effects of a new remedy. Clinical manifestations and the natural history of rheumatic heart disease probably vary in different climates and at different seasons. The supply of cortisone and A.C.T.H. is still limited.

Final judgment on the value of these preparations in the treatment of rheumatic carditis may therefore have to depend upon a critical comparison of small-scale observations made by different workers. We have

pooled our resources of clinical material as well as the supplies of the drugs issued to us through the Liverpool Regional Hospital Board and the Board of Governors of the United Liverpool Hospitals.

Selection of Cases

Our series included cases admitted direct to the hospitals mentioned in the paper, some having been sent to us through the courtesy of colleagues. Two of us (E. N. C. and D. M. F.) are also responsible for 40 children with rheumatic heart disease in St. Joseph's Heart Hospital, Rainhill, and a selection was made of those considered suitable for cortisone therapy. The cases admitted direct to the Royal Southern and Children's Hospitals were generally those showing a fully developed rheumatic carditis, and, in three, necropsy confirmed the clinical diagnosis. In the other cases the signs of active carditis were less conclusive, but were definite enough to justify treatment. The criteria of active carditis will appear from the description of the individual case, and we are aware of the difficulty of proof of diagnosis in certain instances. We have regarded as proof the presence of pericarditis with friction or effusion when there were other rheumatic manifestations and nothing to suggest a non-rheumatic cause such as pneumonia or tuberculosis. If cardiac signs such as murmurs and enlargement were present in a patient with other rheumatic signs and symptoms, the diagnosis was thought permissible.

A combination of some of the following signs was accepted as evidence of the rheumatic state: rheumatic nodules, articular rheumatism, pyrexia, increased sleeping pulse rate, raised sedimentation rate, and rheumatic rashes.

The value of electrocardiographic studies is dealt with in the discussion.

Many cases at first thought suitable for cortisone therapy were discarded because the signs and symptoms of rheumatic carditis subsided without treatment. After strict selection, therefore, we were left with the cases recorded here, in which all three of us agreed there was justification for regarding the carditis as more or less active.

Observations and Treatment

Our purpose was to determine the effects, if any, of cortisone on rheumatic carditis. Many incidental clinical and laboratory investigations were made. In most cases periodic estimations of the red and white cell count (particularly of the eosinophils), the erythrocyte sedimentation rate, and blood electrolyte values were available. For these we are greatly indebted to the pathologists of our respective hospitals—Dr. St. Hill at the Royal Southern Hospital, Dr. Rewell at the Royal Liverpool Children's Hospital, Dr. Brundret at Sefton General Hospital, and Dr. McGinley at Whiston Hospital.

The cardiovascular observations were generally made by each of us independently, but our findings rarely differed. The size of the heart was determined clinically, as it was not justifiable to allow a child with rheumatic carditis to stand for an accurate teloradiogram. On a few occasions portable radiography was used, more to exclude associated pulmonary lesions than to determine the size of the heart. Change in murmurs was noted from day to day, and according to the intensity of the murmur an empirical classification of apical systolic

murmurs into grades 1 to 5 was adopted. Electrocardiographic observations included the standard leads, the unipolar limb leads, and the V leads (2, 4, and 6). Measurements of the P-R and Q-T intervals were nearly all made in standard lead II.

In most cases it was possible to make these investigations once or more often during the control period before the employment of cortisone. We aimed at a minimum of one week for controlled observations before treatment began. In a few cases this was not possible owing to the grave state of the patient on admission. In other cases a much longer period was available before the child was finally selected for treatment. All the cases were in children or adolescents, and the doses of cortisone varied from 50 to 100 mg. daily, spread over periods of ten days to five weeks. In one or two cases larger doses were used. The preparation was "cortone acetate," prepared by Messrs. Merck & Co.

The children were kept under observation for periods of a few weeks to many months, according to the course of the illness.

Case 1

K. O'H. Boy aged 13. (By courtesy of Dr. G. Sanderson.)

History.—February, 1951: appendicectomy; free fluid; no glands; slow recovery. March 6-16: pains in knees and feet and erythematous rash. March 24: severe dyspnoea, irritable unproductive cough aggravating pain in the chest.

Examination on Admission (March 27, 1951).—Pale. Dyspnoea even at rest. Rheumatic nodules on knuckles and left elbow. Erythematous rash fading from trunk. Temperature 100.2° F. (37.9° C.). V.R. 124 to 144. Cardiac impulse 3 in. (7.5 cm.) from midline, forcible and slightly diffuse. Pericardial friction base to apex. Signs of pulmonary consolidation right mid-zone.

Period of Control Observation.—None owing to severity of illness. Before treatment E.S.R. 54 mm., eosinophils 1%.

Period of Cortisone Treatment (March 28 until April 4).—Dosage 100 mg. daily. At first there was a slight improvement in general condition, but this soon worsened. Pericardial friction was unchanged and pulmonary consolidation extended. E.S.R. remained at 52 mm., but there was a slight fall in temperature and heart rate. Only one E.C.G. was taken. QTc interval 0.45. Death on April 4.

Necropsy (Dr. Charles St. Hill).—Severe rheumatic carditis with fibrinous pericarditis but no increase in fluid. Recent vegetations on mitral and aortic valves. Sections showed areas of round-cell infiltration in myocardium but no Aschoff nodules. Greater part of both lungs completely solid but dry.

Conclusions.—Fulminating case of rheumatic carditis uninfluenced by cortisone. Fluid imbalance was present when cortisone was first given and necropsy showed only slight evidence of fluid retention.

Case 2

J. H. Boy aged 13. (By courtesy of Dr. White Jones.)

History.—Ill for three months before admission with anorexia, fatigue, and pains in joints without objective signs. Occasional pyrexia.

Examination on Admission (March 29, 1951).—Pallor. Nodules on occiput only. Slight swelling both knees with effusion into the left. Great pain on movement of left hip. V.R. 120. E.S.R. 33 mm. Pulse collapsing. B.P. 95/40. A.B. not unduly forcible and normal in position. Grade 3 apical systolic murmur; loud long blowing aortic diastolic murmur over base of heart and downwards to left of sternum. Active carditis was thought probable but not proved.

Period of Control Observation (March 29-April 6).—Temperature ranged from 98.4 to 101° F. (36.9 to 38.3° C.). Sleeping pulse rate 90 to 120. E.S.R. 19 to 21 mm. The

joint manifestations continued; no new nodules appeared. A doubtful apical diastolic and a soft aortic systolic murmur appeared. April 3: P-R 0.15, QTc 0.45 April 5: P-R 0.16, QTc 0.44.

Period of Cortisone Treatment (April 7-16).—Dosage: first day 200 mg.; next six days 100 mg.; last six days 50 mg. General improvement, subsidence of joint signs, fall of E.S.R. to 9 mm. and of V.R. to 90 within a week. No significant change in clinical cardiac signs. April 10: P-R 0.13, QTc 0.44. April 13: P-R 0.14, QTc 0.44. Eosinophil count unexpectedly rose during treatment.

Period of Subsequent Observation (April 17-July 22). For four weeks there was general improvement except for a short return of articular rheumatism from April 23 to 28. Sleeping pulse rate ranged from 88 to 110, but E.S.R. gradually rose to 20 mm. Clinical heart signs virtually unchanged. Fullness of the face was noted two weeks after cortisone was discontinued and persisted for 10 days. Condition remained fairly satisfactory until June 21, when pericarditis appeared, followed by congestive heart failure and death on July 22.

Necropsy.—Rheumatic lesions of mitral, tricuspid, and aortic valves with pericardial, pleural, and peritoneal effusions.

Conclusions.—The course of the illness suggests that active carditis was responsible for the final development of cardiac failure. Cortisone controlled the rheumatic manifestations for a few weeks, though it is not certain if it affected the carditis. On the other hand, it was not held responsible for aggravation of the cardiac failure, as this appeared five weeks after the drug was discontinued.

Case 3

E. L. Girl aged 8. (By courtesy of Dr. R. W. Brookfield and Dr. R. R. Hughes.)

History and Examination on Admission (November 30, 1950).—Pains in abdomen, chest, and legs. Loss of weight. Anorexia and nausea for two weeks. Child very ill. Temperature 101.4° F. (38.6° C.), V.R. 186, respirations 76. Rough apical systolic murmur. Signs of consolidation in left lower zone.

Period of Control Observation (November 30-December 8).—The patient was not specially selected for cortisone treatment, but as other measures had failed to influence the illness, which was provisionally diagnosed as acute rheumatic carditis, cortisone was thought worthy of trial. Before cortisone the general condition and cardiac signs remained unchanged. Temperature averaged about 99° F. (37.2° C.), but V.R. ranged from 138 to 156. By December 9 the general condition was deteriorating and cyanosis and hepatic enlargement were noted.

Period of Cortisone Treatment (December 9-January 1).—Dosage: December 9-15, 100 mg. daily; December 16-20, 50 mg.; December 20-January 1, 25 mg. The temperature remained just over normal. The sleeping pulse rate fell to 120-140, but there was no change in the heart signs or general condition. Fluid balance was unsatisfactory, but no record was available for comparison before cortisone was started. December 10: P-R 0.12, QTc 0.42. December 18: P-R 0.14, QTc 0.45. Death occurred on January 1, 1951.

Necropsy (Dr. Charles St. Hill).—Acute rheumatic carditis. Cellular infiltration of myocardium with Aschoff nodules. Vegetations on mitral and aortic valves. Old and new pericarditis. Congestive changes in lungs and liver.

Conclusions.—Cortisone did not modify the course of the disease.

Case 4

M. J. Girl aged 6. (By courtesy of Dr. White Jones.)

History.—Well until one month before admission. Joint pains, fever, and cough appeared, and cardiac enlargement, with a loud apical systolic murmur, was noted. Some improvement occurred with salicylates.

Examination on Admission (June 16, 1951).—Looked ill but good nutrition. Two rheumatic nodules on occiput. No joint manifestations or evidence of cardiac failure. V.R. 125. Cardiac thrust diffuse and turbulent. Grade 4 apical systolic murmur.

Period of Control Observation (June 16-20).—Pending availability of cortisone, salicylates and penicillin were given. In spite of them pyrexia of 100-102° F. (37.8-38.9° C.) continued with raised E.S.R. (22-23) and tachycardia (100-116). No signs of arthritis, or further nodules. Clinical heart signs unaltered. No E.C.G. taken. Signs of mild congestive heart failure and of pulmonary consolidation developed.

Period of Cortisone Treatment (June 20-July 3).—Dosage: First and second days, 500 mg. daily; then four daily doses of 100 mg. and 50 mg. daily for another eight days. Penicillin was continued in view of the uncertain nature of the pulmonary consolidation. Temperature became normal by the third day and E.S.R. fell steadily to 11 mm. on the thirteenth day. Slight initial general improvement was masked by signs of fluid retention, which was treated on the eighth day by mercurials followed by considerable improvement. Chest clear by the eleventh day. Sleeping pulse kept about 90 after third day of treatment. No change in clinical heart signs except disappearance of extrasystoles and less cardiac tumult. June 23: P-R 0.15, QTc 0.42. June 28: P-R 0.16, QTc 0.40. Eosinophils fell from 0.44 to 0.19%.

Period of Subsequent Observation (July 4-September 4).—Four days after cortisone was stopped there was a return of fever, tachycardia, and cardiac tumult, but no arthritis or nodules. Salicylates controlled the temperature but not the heart rate. Signs of heart failure appeared temporarily, but subsided in the second week of this period. Thereafter the condition remained satisfactory for the remaining six weeks in hospital and for four months subsequent to discharge. No significant change in the E.C.G. during this period.

Conclusions.—Evidence pointed to severe active carditis with pneumonic consolidation, not affected by salicylates or penicillin but showing temporary improvement with cortisone and control of water retention. Relapse soon after cessation of cortisone, but, later, spontaneous improvement.

Case 5

J. W. Boy aged 13.

History.—Ten days before admission: tonsillitis followed by articular rheumatism. Four previous attacks of rheumatism since aged 7.

Examination on Admission (April 6, 1951).—Subjective and objective evidence of articular rheumatism. No nodules or rash. Temperature normal. V.R. 100. B.P. 110/50. A.B. diffuse within nipple line. Grade 3 apical systolic murmur. Doubtful apical diastolic.

Period of Control Observation (April 7-19).—Pyrexia at first and development of rheumatic nodules. Further joint involvement and signs of pulmonary consolidation at right base (for which penicillin was used empirically). Later apex beat moved outside nipple line, and pericardial friction developed on April 13, being widespread by April 19. April 17: P-R 0.20, QTc 0.42, low voltage QRS leads I, aVR, aVL, and V₁.

Period of Cortisone Treatment (April 19-29).—First dose 200 mg., 100 mg. daily on 10 subsequent days. Temperature gradually fell to normal; there was much improvement in the general condition and the lung signs diminished, but the E.S.R. did not fall appreciably (23 to 20). The sleeping pulse fell at first, then rose; the cardiac signs remained unchanged. E.C.G. on April 20, 23, and 27: P-R 0.16; QTc 0.41, 0.47, 0.44. The eosinophil count fell. On the eighth day of treatment signs of fluid retention appeared, and for safety cortisone was discontinued on April 29.

Period of Subsequent Observation (April 30–June 21).—The condition worsened on April 30 with increased dyspnoea, increased respiratory rate, and tachycardia (140). Mersalyl with restriction of fluids was prescribed. By May 4 there were no longer any signs of cardiac failure, fluid retention, or active carditis. Pericardial friction had disappeared but murmurs still present. E.C.G. (May 8) T inverted leads I and V_3 , P-R 0.14, QTc 0.42. A streptococcal throat infection then occurred, followed by arthritis and nodules but no further cardiac signs. The acute symptoms subsided with penicillin followed by salicylates, which were continued for 13 weeks. By June 21 there was great general improvement, normal E.S.R. and heart rate, but no change in the heart signs. May 22: P-R 0.14, QTc 0.42. June 1: P-R 0.12, QTc 0.41. The child was seen again December, 1951. He was resuming moderate physical activity and no further signs of rheumatism or carditis had occurred.

Conclusions.—Cortisone seemed to have resulted in improvement in general health, but may have contributed to water retention. This was quickly controlled and the evidence of active carditis disappeared coincidentally.

Case 6

J. R. Boy aged 16.

History.—February 8, 1951, sore throat, which returned on March 3 accompanied by stiffness in joints and slight pyrexia. Apical systolic murmur noted (Dr. Prideaux).

Examination on Admission (March 21, 1951).—Rather pale and ill. Bilateral effusions in knee-joints.

Period of Control Observation (March 21–27).—Slight pyrexia with normal pulse rate. Signs of articular rheumatism persisted. Clinical evidence of slight cardiac enlargement with Grade 2 apical systolic murmur. Very doubtful apical diastolic. E.S.R. 59 mm. and 50 mm. Water balance normal. P-R 0.16 to 0.18, QTc 0.36 to 0.38.

Period of Cortisone Treatment (March 27 to May 3).—200 mg. followed by 100 mg. daily until April 3, then 50 mg. daily until April 12, a further 100 mg. daily April 13 to 17, 50 mg. daily until April 27, and, finally, 25 mg. until May 3. Within three days pyrexia and joint symptoms subsided and there was much improvement in general condition. E.S.R. fell (Fig. 1). Cardiac signs unchanged though occa-

FIG. 1.—Case J. R. Effect of cortisone on the rheumatic state.

sionally Carey Coombs murmur was audible, disappearing towards end of treatment. P-R varied from 0.14 to 0.20, and QTc from 0.38 to 0.45. Slight fullness in face and increase in abdominal girth appeared without oedema or disturbance of fluid balance. Articular manifestations recurred with smaller dosage of cortisone, but after second course of higher dosage rheumatic state finally subsided.

Period of Subsequent Observation (May 3 to July 13).—Slight return of articular rheumatism controlled by salicylates; otherwise general improvement. Slight recession in position of cardiac impulse and lessening in intensity of apical systolic murmur. No further diastolic. P-R 0.20, QTc 0.40 (May 10). Continued increase in weight after cortisone, finally reverting to normal proportions in autumn. November, 1951, no evidence of organic valvular lesion.

Conclusions.—Cortisone effected great improvement in rheumatic state, but disappearance of cardiac signs may not have meant more than the coincident decrease in size of left ventricle. The case was interesting in suggesting that increase of weight could be due to obesity rather than fluid retention.

Case 7

D. L. Girl aged 15. (By courtesy of Professor N. B. Capon.)

History.—Tonsillitis four weeks and articular rheumatism four days before admission.

Examination on Admission (April 4, 1951).—Pale, sweating, and temperature 101.8° F. (38.8° C.), acute rheumatism in knees and right ankle. V.R. 80. No cardiac enlargement. No murmurs.

Period of Control Observation (April 4–9).—Temperature varied from 101 to 103° F. (38.3 to 39.4° C.), with E.S.R. 23 to 24 mm. Articular rheumatism moved to elbows, wrists, and other joints. Sleeping pulse rather slower. Slight outward movement of cardiac impulse and precordial heaving. Grade 2 apical systolic murmur developed. P-R 0.12, QTc 0.42.

Period of Cortisone Treatment (June 10–24).—Daily dosage 200 mg. for two days, 100 mg. for eleven days, and 50 mg. for another two days. Much general improvement with subsidence of fever and articular signs within a week. E.S.R. fell from 24 to 14. Sleeping pulse from 88 to 44. Cardiac impulse receded slightly but murmurs were unchanged. June 21: P-R 0.14, QTc 0.42.

Period of Subsequent Observation (June 25 to November 26).—Improvement continued for one week; then recurrence of articular rheumatism but no fresh cardiac signs. Apical systolic murmur had disappeared. Condition controlled in a few days by salicylates. In the next four months child remained well except for minor febrile episodes, but soft aortic diastolic murmur appeared in August.

Conclusions.—Cortisone benefited the rheumatic fever and possibly the cardiac changes at first but did not prevent the subsequent development of slight aortic incompetence.

Case 8

S. B. Girl aged 11.

History.—Under observation St. Joseph's Heart Hospital one year. Poor general condition, moderately loud apical systolic murmur and doubtful apical diastolic. May, 1950: severe rheumatic fever with pericarditis followed by mild congestive heart failure. Aortic diastolic murmur noted August, 1950. Then improvement. Recurrence of rheumatic state February, 1951, but no fresh heart signs.

Examination on Admission (February 5, 1951).—Signs of mitral and aortic disease unchanged. No evidence of failure. Pallor, tachycardia, and E.S.R. 17 mm.

Period of Control Observation (February 5–14).—Signs of active rheumatic process gradually subsiding. Cardiac murmurs unchanged. February 12: P-R 0.16, QTc 0.45.

Period of Cortisone Treatment (February 14–24).—First dose 100 mg., subsequently 50 mg. daily. No change in cardiac signs or E.C.G. measurements.

Period of Subsequent Observation.—February 24 to March 20: condition unchanged. March 20, 1951, to March, 1952: general condition at first good with heart signs unchanged, but for the last few months tendency to tachycardia without any fresh rheumatic or cardiac manifestations.

Conclusions.—The carditis in this case, though originally severe, was mild when cortisone therapy was started. The treatment did not modify the condition or arrest the progress of the cardiac signs. The small doses used did not modify body contour or lead to water retention.

Case 9

K. G. J. Boy aged 10. (By courtesy of Dr. Angelman.)

History.—Warrington General Hospital, February 22 to March 28, 1951, with rheumatic fever, apical systolic and doubtful diastolic murmur, and rheumatic nodules. Transferred to Royal Southern Hospital.

Examination on Admission (March 28, 1951).—A few nodules still present. Grade 3 apical systolic murmur. Doubtful apical diastolic.

Period of Control Observation (March 26 to April 12).—Temperature slightly raised at first, falling later. E.S.R. 47–48 mm. initially, falling to 20 later. Cardiac signs unchanged though the diastolic murmur became more obvious. P–R 0.13 to 0.14, QTc 0.41 to 0.44.

Period of Cortisone Treatment (April 13–26).—Seven daily doses of 100 mg., followed by seven of 50 mg. No pyrexia (already normal in control period). Sleeping pulse gradually fell from 100 to 60. E.S.R. fell to 8 mm. after cortisone ceased. No appreciable change in cardiac signs. P–R 0.12, QTc 0.42 and 0.38. Water balance normal; voracious appetite and increase in weight.

Period of Subsequent Observation.—Four days after cortisone was discontinued, reactivity of rheumatic state with pyrexia, tachycardia, and rise of E.S.R. Apical systolic murmur grades 3 to 4. Doubtful short presystolic murmur. May 3: P–R 0.12, QTc 0.42. Child seen several times between May and October, 1951. No further rheumatic manifestations, and heart signs unchanged.

Conclusions.—Clear rheumatic fever but cardiac signs probably subsiding at time of cortisone therapy. No alteration in heart signs under treatment, except bradycardia.

Case 10

V. P. Girl aged 10. (By courtesy of Dr. White Jones.)

History.—Articular pains and listlessness December, 1950, for two weeks. Then well for two months.

Examination on Admission (March 2, 1951).—Rather frail child; temperature 99° F. (37.2° C.); two small nodules on occiput. Joints normal. E.S.R. 20. V.R. 88. Slight cardiac enlargement. Blowing apical systolic and apical diastolic murmurs, also faint aortic diastolic to left of sternum. B.P. 135/58. P–R 0.16, QTc 0.40.

Period of Control Observation (March 3–14).—No manifestations of rheumatism. E.S.R. fell from 20 to 17. No change in cardiac signs. Slight rise in QTc to 0.46.

Period of Cortisone Treatment (March 15–26).—First day 200 mg.; subsequently 100 mg. daily. E.S.R. fell further to 11. No change in cardiac signs, except slight recession of apex. QTc 0.365.

Period of Subsequent Observation (March 27 to December 7).—General condition remained good. Occasional slight pyrexia and rise of E.S.R. to 18 on April 5. Cardiac murmurs unchanged.

Conclusions.—General improvement with fall in E.S.R. but no definite change in cardiac state under influence of cortisone.

Case 11

E. H. Girl aged 14.

History.—Three attacks of tonsillitis, December, 1950, to February, 1951. Two weeks after the last fever and articular rheumatism.

Examination on Admission (March 21, 1951).—Temperature 100.2° F. (37.9° C.). Tonsils large, not obviously infected. Rheumatic nodules on hands, scapula, and occiput. Objective evidence of articular rheumatism, ankles, hands, and wrists. Sleeping pulse 100. No cardiac enlargement. Soft apical systolic murmur (grade 1). P–R 0.2, QTc 0.43. QRS low voltage lead I and AVL.

Period of Control Observation (March 21–April 2).—Pyrexia and joint manifestations subsided but several fresh nodules appeared. Sleeping pulse tended to fall, averaging 82 on last four nights. No further cardiac signs. P–R 0.16, QTc 0.40. E.S.R. readings 17–20 mm.

Period of Cortisone Treatment (April 3–17).—Initial dose 200 mg. followed by 100 mg. daily for 14 days. Temperature never above 99° F. (37.2° C.). E.S.R. fell to 9. Nodules became smaller. Sleeping pulse averaged 52 in second week. Heart signs unchanged. E.C.G. increased voltage in lead I; QTc 0.39.

Period of Subsequent Observation (April 18–November 15).—Condition satisfactory until further tonsillitis April 27. Some joint pains but no further objective signs. No change in heart but new nodules appeared on May 5 and 7. Thereafter satisfactory progress.

Conclusions.—Cortisone accompanied by general improvement and fall in E.S.R. and lessening in nodules. No clear proof of carditis in this case.

Case 12

A. M. Boy aged 8. (By courtesy of Dr. White Jones and Professor N. B. Capon.)

History.—Fever and articular rheumatism 18 days before admission. Partial response to calcium aspirin. Erythema marginatum developed on legs.

Examination on Admission (May 7, 1951).—Objective signs of articular rheumatism still present. Some muscular wasting. V.R. 128. No cardiac enlargement. Apical systolic murmur grade 1–2. B.P. 115/55.

Period of Control Observation (May 7–13).—Pyrexia subsided to 99° F. (37.2° C.), but rheumatism in knees remained unchanged. E.S.R. on several occasions 23. Sleeping pulse fell slightly. Cardiac signs unchanged. P–R 0.12, QTc 0.42. Doubt existed whether the diagnosis was early Still's disease or rheumatic fever. Evidence of cardiac involvement very doubtful.

Period of Cortisone Treatment (May 14–27).—First had 200 mg., next seven days 100 mg., and last six days 50 mg. daily. Temperature normal May 15 and thereafter. E.S.R. fell to 10. Rapid improvement in joints, but left knee-joint remained enlarged and limited in movement. Much improvement in general condition. Sleeping pulse averaged 75 during second week of treatment. No alteration in cardiac state. QTc increased to 0.45, 0.445, and 0.45 in successive records. After eight days' treatment some evidence of fluid retention, which decreased with lessened dose of cortisone. Appetite always good but ravenous during treatment. Gain in weight maintained for three weeks after cessation of cortisone.

Period of Subsequent Observation (May 29–November 22).—After withdrawal of cortisone there was a return of articular rheumatism, pyrexia, and a rise in E.S.R. The apex beat appeared to have moved out slightly. Heart sounds unaltered. QTc 0.425. Salicylates were thereafter employed with considerable improvement. Cardiac murmur and evidence of enlargement disappeared after four weeks. P–R 0.14, QTc 0.42 and 0.43.

Conclusions.—Case finally accepted as one of Still's disease. Joint manifestations and general condition improved by cortisone. No alteration in state of heart.

Discussion of Results

For analysis of the results it seems necessary to separate those severe cases of undoubted carditis from those in which

the cardiac signs were less convincing though there may have been clear evidence of a rheumatic state. The 12 cases which received treatment can be divided into two groups—five in which the lesion was severe (three fatal), and seven in which rheumatic fever with probable involvement of the heart was present in a milder form.

The term "rheumatic fever" is used as being synonymous with the rheumatic state—that is, to include manifestations such as fever with articular involvement, subcutaneous nodules, or rheumatic rashes. It was hoped that the less severe cases might give important information about the optimum dosage of cortisone, for in the severe cases it seemed that large doses were most likely to be effective. Further, we were anxious to find not only whether cortisone would arrest a fulminating type of carditis but also whether it would modify the course in cases of grumbling infection.

In determining the beneficial effects of any treatment difficulty is encountered because of our imperfect knowledge of the natural history of rheumatic fever and especially of rheumatic carditis. Such a sign as pericardial friction is well known to last for days or weeks, or to be completely absent in a case which subsequently proves at necropsy to have extensive pericarditis. Similarly, rheumatic nodules may last a few days only, or may be present for many weeks, and it is sometimes difficult to determine which are new and which are old. Murmurs are notoriously inconstant and are modified by fever, tachycardia, and cardiac dilatation, all of which may wax and wane. The erythrocyte sedimentation rate provides a useful indicator of the course of the rheumatic state, always assuming that non-rheumatic causes for its rise can be excluded.

In assessing these physical signs, therefore, it would be unjustifiable to conclude that *minor* variations in them had any great significance.

The electrocardiographic studies might be expected to give more precise evidence of myocardial involvement. In our experience the information yielded was disappointing. With a clear clinical picture of active rheumatic carditis it is common to have a normal electrocardiogram, and even when the P-R or Q-T interval is lengthened it is not always evidence of myocardial disease. Further investigations on Q-T measurements are necessary before assessing the value of this measurement in active carditis.

Fox *et al.* (1950), for example, observed the phenomenon rather frequently in childhood tuberculosis, and, though Craige *et al.* (1950) noted that the Q-T interval was above the average normal in 29 cases of fatal pancarditis, the level reached was not above the upper limits of normal, and, while generally the changes in the Q-T interval and clinical manifestations of rheumatic fever ran parallel, there were some instances in which they took opposite directions. On the other hand, Taram and Szilagyi (1951), in a large series of cases, found a close relationship between the length of the Q-T interval and the extent of the cardiac disability.

Thus it is clear that an appropriate grouping of signs is necessary before the diagnosis is established, and that physicians may vary to some extent regarding the combination of signs by which they justify the diagnosis. In order that readers may be familiar with the signs which we ourselves have accepted, it was thought advisable to summarize each individual case. Once the pattern of rheumatic carditis has been agreed upon, modifications in that pattern may be regarded as the result of treatment if they were not likely to have occurred in the same period of time without therapy.

In our series two of the rapidly fatal cases showed no appreciable change in the cardiac state during the use of cortisone, nor was there any certain evidence that the drug worsened the condition. It may well have been that such fulminating cases could scarcely have been expected to respond to any form of therapy, and that, on the other hand, the short duration of the illness made it impossible to determine whether cortisone had any ill effects. In one

of the fatal cases (No. 1) clinical evidence of pulmonary consolidation was present and the possibility of pulmonary oedema precipitated or aggravated by cortisone was considered, but at necropsy the lungs proved to be quite dry.

In another fatal case (No. 2) there was some improvement in the general condition and articular rheumatism but no material alteration in the cardiac signs. It was clear from the progression of the illness through the stage of congestive heart failure to death, after the cessation of cortisone administration, that the cortisone did not arrest the activity of the carditis which was held to be responsible. Again, it seems improbable that the cardiac failure was precipitated by cortisone therapy in view of the time of its appearance.

In contrast with the fatal cases two others of considerable severity still survive. In Case 4 the diagnosis of carditis was complicated by pneumonia, which was treated with penicillin during the period of control observation. During the same period signs of mild congestive heart failure also appeared. In view of the beneficial results claimed by Bell *et al.* (1950) (in a similar case) for large initial doses of cortisone, two daily doses of 500 mg. were given, followed by lessening doses for 12 days. There was some initial general improvement, but this was masked by water retention, which was controlled by mercurial injections. When the cortisone was discontinued pyrexia returned with a high sleeping pulse rate and cardiac tumult which were unmodified by administration of salicylates.

Case 5 presented somewhat similar features. These two cases illustrate the risk of water retention when cortisone is used in cases with severe carditis, though it would appear that this adverse effect can be controlled by mercurial diuretics. The improvement in the general condition in such cases does not of course indicate any alteration in the carditis, but it may help to sustain the patient over a period of danger. In order to produce even this limited effect, however, it is clear that a careful balance must be maintained between the dosage of cortisone and the use of mercurial diuretics if water retention becomes apparent.

Any improvement recorded had only a brief duration after the cortisone was discontinued, but it is possible that this disadvantage may be overcome by the use of cortisone in smaller doses and over a much longer period. Prolonged administration would probably require periodic diuresis by mercurials and avoidance of dangerous disturbances of the blood electrolytes.

Amongst the milder cases treated there was a general tendency to physical improvement, but in no case were the heart signs conclusively modified.

In Case 6, which was under prolonged observation, it was evident that while a dose of 100 mg. of cortisone daily was adequate to control the fever and joint manifestations and reduce the E.S.R., 50 mg. daily was unable to achieve this. This case also formed an interesting contrast with Cases 2 and 4, in which water retention occurred. The boy developed the same puffiness of the face and increased in weight, but there was no significant change in the fluid balance, and as time passed the texture of the subcutaneous tissues suggested there was an increase in fat.

In this and other cases a voracious appetite during the administration of cortisone disappeared a week or two after the drug was stopped. It seemed reasonable to assume that the increase in weight was partly due to this fact and that it would not be justifiable to conclude that facial swelling and increasing weight were always evidence of water retention.

When the individual signs are compared during the control and cortisone periods the following points emerge:

1. *Cardiac Signs.*—There were no modifications in the heart signs which could be regarded as *conclusive* evidence of benefit from the drug, though in Cases 2 and 6 apical

FIG. 2.—Effect of cortisone on sleep pulse rate in active carditis. Shaded areas indicate period of cortisone administration. (In Case J. R. only the average pulse rate was available.)

systolic murmurs became less intense and diastolic murmurs, probably of the Carey Coombs type, disappeared or became less evident.

2. *Heart Rate.*—There was a clear fall in the heart rate in several cases, sometimes independent of, or greater than, any fall in temperature. This is shown clearly in Fig. 2, and is especially pronounced in Case 7, in which the rate fell to levels below 50.

3. *E.C.G. Changes.*—The P-R interval varied in the control period from 0.12 to 0.19 and during the period of cortisone treatment from 0.12 to 0.18. These quite wide variations gave little justification for assuming in the individual cases that cortisone modified this measurement. In three of the cases the P-R interval shortened during treatment, but in two cases it lengthened. Similarly, the QTc varied from 0.36 to 0.44 during the control period, and during cortisone administration from 0.40 to 0.45. In one case (No. 8) the QTc fell from 0.44 to 0.42 during treatment and rose subsequently to 0.43, but in Case 6 the measurement actually increased during cortisone therapy from 0.36 to 0.41, falling to 0.40 when treatment was discontinued. None of these electrocardiographic changes can therefore be considered of proved importance.

Effect of Cortisone on P-R and QTc Intervals

P-R Interval				QTc Interval			
Case	Control Period	Cortisone Administration	Subsequent Observation	Case	Control Period	Cortisone Administration	Subsequent Observation
K. G. J.	0.135	0.12	0.12	K. G. J.	0.43	0.41	0.40
S. B.	0.160	0.16	0.16	S. B.	0.45	0.425	0.43
K. O'H.	—	0.18	—	K. O'H.	—	0.45	—
E. L.	0.12	0.14	—	E. L.	0.42	0.45	—
J. R.	0.16	0.16	0.20	J. R.	0.36	0.41	0.40
J. H.	0.155	0.135	0.14	J. H.	0.44	0.44	0.44
D. L.	0.12	0.14	0.13	D. L.	0.42	0.42	0.395
J. W.	—	0.18	0.14	J. W.	—	0.43	0.43
E. H.	0.19	0.16	—	E. H.	0.41	0.41	—
V. P.	0.16	0.16	0.16	V. P.	0.415	0.41	0.40
A. M.	0.12	0.12	0.12	A. M.	0.42	0.45	0.44
M. J.	—	0.16	0.13	M. J.	—	0.41	0.4000

4. *Erythrocyte Sedimentation Rate.*—This was estimated when possible by Wintrobe's method, but it was often necessary to use the micro-method, and the figure was doubled for rough comparison with the macro-method. All figures in the text are micro-method unless specified. Fig. 3 shows distinctly that the sedimentation rate falls in a considerable percentage of cases during cortisone administration. But

FIG. 3.—Effect of cortisone on erythrocyte sedimentation rate in active carditis. As the micro-method only was available in certain cases, and in the others estimation was made by Wintrobe's method, the Wintrobe figures have been regarded as equivalent to twice the micro-method values. Shaded areas indicate the period of cortisone administration.

without corresponding improvement in cardiac signs this cannot be held to mean more than the lessening of an infective process, in these cases the rheumatic state.

5. *Eosinophil Count.*—The fall in the eosinophils has no particular significance in relation to rheumatic carditis, but the count was important as a control observation to make sure that the drug was active. Although a fall was not constant, we were satisfied that it occurred often enough on use of the same batch of cortisone.

6. *Improvement in the General State of Health.*—This was observed in several cases, even at times in the very severe forms of the disease. The improvement took the form of increased appetite, liveliness, a better colour, and better sleep. These beneficial signs were in some instances accompanied by disappearance of the articular manifestations and less certainly in the regression of rheumatic nodules. If general ill-health is an important clinical aspect of the rheumatic state, benefit may reasonably be claimed for the cortisone in this direction.

Summary

Twelve cases of rheumatic carditis, all in children, were treated with cortisone. In one the diagnosis was later revised to Still's disease, but as there was some doubt about the presence of carditis treatment was continued.

Three cases were fatal. Two were fulminating in character and the diagnosis of active rheumatic carditis was confirmed at necropsy. Cortisone was tried as a life-saving measure but without success. The third case showed some temporary improvement in the general condition, but cardiac failure and death followed two months later.

The other nine cases showed some evidence of carditis, varying from severe to mild. In none of them was there clear evidence of improvement in the cardiac signs, either clinical or electrocardiographic.

Except in the fatal cases there was usually some improvement in the general condition. The patient's mental well-being improved, as also did the skin colour and appetite. Most notable, however, was the tendency for the heart rate to slow, sometimes irrespective of a fall in temperature.

In several cases, fullness of the face suggestive of oedema, increase in abdominal girth, and sometimes very slight sacral oedema were noted. These cases were regarded with suspicion as possibly resulting from water retention due to the effects of cortisone. They occurred chiefly in cases with severe carditis, and in the milder cases similar doses of cortisone did not appear to have the same result. There was always an element of doubt, therefore, about how far the apparent water retention was due to cardiac failure and how far to the administration of the drug, but it was thought wise on occasion to use mercurial diuretics. In this small series of cases the blood electrolyte values were not very helpful, and in those children who were gravely ill the measurement of fluid intake and output had practical difficulties which diminished its accuracy.

It would appear that fullness of the face and abdomen was not always due to water retention, as it might occur without any disturbance of the fluid balance or blood electrolytes. In these cases the texture of the subcutaneous tissues, particularly the abdominal wall, suggested increased deposition of fat and was often associated with a voracious appetite, during and for some time after cortisone administration.

The investigations confirmed the results of other workers—that cortisone exerts a beneficial effect upon non-cardiac manifestations of rheumatic fever—for example, pyrexia, raised sedimentation rate, and articular inflammation—though it is doubtful if the joints respond more favourably than to salicylates.

The dosage of cortisone varied from 50 mg. to 500 mg. daily over periods of a few days to a few weeks. A fall in the eosinophil count was taken as evidence that the particular batch of cortisone was active.

The results of cortisone treatment were, on the whole, disappointing, and high dosage did not appear to achieve anything more than moderate dosage and carried with it a greater risk of side-effects. Whilst admitting the lack of any spectacular response, we think that the improvement in the patient's general condition and the tendency to slowing of the heart justify further investigation. It would appear that more information is necessary about the effects of prolonged administration of small doses, particularly if there is an initial beneficial response to moderate doses. Such treatment would obviously need careful supervision, cautious dosage, and the use of mercurial diuretics from time to time, if necessary.

We wish to express our appreciation of the help from our colleagues, both medical and nursing. In particular we would like to thank our medical registrars—Dr. McKendrick, Dr. Anderton, Dr. Jones, Dr. Ellenbogen, and Dr. Coulshed—and the resident medical officers of our various hospitals. For electrocardiographic records we are indebted to the careful work of Mr. E. Caldwell.

NOTE.—The case histories, in fuller and more detailed form, will be available on duplicated sheets from the office of the *British Medical Journal* to those who express a special interest in having them.

REFERENCES

- Barnes, A. R., and Smith, H. L. (1950). *Mod. Conc. cardio-vasc. Dis.*, 19, 59.
 Bell, G. I., Bell, R. E., and Wilson, D. R. (1950). *Canad. med. Ass. J.*, 63, 63.
 Coste, F., et al. (1950). *Bull. Soc. méd. Hôp. Paris*, 66, 1577.
 Craig, E., et al. (1950). *Circulation*, 1, 1338.
 Fox, T. T., et al. (1950). *Ibid.*, 1, 1184.
 Harris, T. N., et al. (1951). *Ibid.*, 3, 215.
 Hench, P. S., Kendall, E. C., et al. (1950). *Arch. intern. Med.*, 85, 545.
 ———, Slocumb, C. H., et al. (1949). *Proc. Mayo Clin.*, 24, 277.
 Keith, John D., and Neill, C. A. (1951). *Canad. med. Ass. J.*, 64, 193.
 McEwen, C., et al. (1950). *Bull. N.Y. Acad. Med.*, 26, 212.
 Taram, L. M., and Szilagyi, N. (1951). *Brit. Heart J.*, 13, 10.
 Videbaek, A., et al. (1950). *Acta endocrinol.*, 4, 245.

SOME CONCEPTS OF RHEUMATIC DISEASE*

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The normal and morbid anatomy of the connective tissues at the molecular level has been discussed in some detail because it is at this level, where structure and function are inseparable, that the essential processes of life arise, and because I believe that it is through discoveries at this level that revolutionary advances in our understanding of the rheumatic diseases are likely to take place.

At the clinical level patients suffering from the rheumatic diseases present a variety of disorders of structure and function, and we will now examine some of these disorders more closely to see whether or not they can be fitted into a concept of rheumatic diseases based upon the assumption that these diseases result from primary connective-tissue lesions.

Some of the most prominent features of two typical rheumatic diseases, such as rheumatoid arthritis and degenerative joint disease, are set out in Table I. The

TABLE I

Clinical Features	Rheumatoid Disease	Degenerative Joint Disease
Connective tissue lesions	Widespread, often symmetrical, affecting joints, tendons, bones, muscles, skin, viscera, eyes, and other structures. Resulting in marked atrophy and destruction of all affected structures	Often localized to one or more joints, resulting in loss of cartilage and bone in pressure zones with marginal overgrowth
Serum factor agglutinating sensitized sheep cells	Present in high titre in most cases	No more than normal
Loss of body weight	Marked, particularly during exacerbations of disease	None
Inflammatory reaction	Marked, both locally in connective tissues as well as systemically	Very little if at all, and only locally in joints
Lymphadenopathy	Frequent, particularly in young subjects; occasional splenomegaly	None
Anaemia	Frequent, particularly during exacerbation of disease	"
Personality changes	Frequent during exacerbation of disease	"
Increased sweating and peripheral vascular disorders	Marked, particularly during exacerbation of disease	"
Course of disease	Very variable with many unexpected exacerbations and remissions	Usually slowly progressive

clinical features of degenerative joint disease clearly result from the initial cartilage lesion, but the manifold features of rheumatoid disease present a more complex problem. But before discussing the various features of rheumatoid disease it would be as well to define this clinico-pathological entity. In many countries, and particularly in America, the term has been used to embrace all forms of polyarthritis of obscure aetiology, so including ankylosing spondylitis, psoriatic arthropathy, Reiter's disease, and many other polyarthritic syndromes, as well as the classical form of rheumatoid disease with symmetrical peripheral joint involvement, widespread soft-tissue changes, and other features mentioned in Table I.

*The second Goulstonian Lecture, given at the Royal College of Physicians of London on January 17. The first lecture was published in our previous issue.